A Stereoselective Approach for the Synthesis of α-Sialosides

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A highly efficient synthesis of the human melanoma associated antigen GD_3 derivative has been described. A key feature of the synthetic approach was the use of sialyl donors that were protected with a C-5 trifluoroacetamide moiety. These sialyl donors gave high yields and excellent α-anomeric selectivities in direct glycosylations with a wide variety of glycosyl acceptors ranging from C-8 hydroxyls of sialic acids and C-3 hydroxyls of galactosides to reactive primary alcohols.

Introduction

Sialic acids are a diverse family of naturally occurring 2-keto-3-deoxy-nononic acids that are involved in a wide range of biological processes.[1,2] The most abundant sialic acid derivative is *N*-acetylneuraminic acid (Neu5Ac); however, compounds that have a glycolyl moiety at the C-5 amino group (Neu5Gc) or acetyl esters at one or more hydroxyls are also frequently encountered in nature.[1,3] Sialic acids normally appear at terminal positions of oligosaccharides of glycoproteins and glycolipids where they are α(2,3) or α(2,6) linked to galactosides or α(2,6) linked to 2-acetamido-2-deoxy-galactosides. The disialosyl structures Neu5Acα(2-8)Neu5Ac and Neu5Acα(2-9)-Neu5Ac have also been found as constituents of oligosaccharides of glycoproteins and lipids. These substructures are receptors for viruses and bacteria and constitute the immunodominant epitope of tumor-associated antigens. Neu5Ac or Neu5Gc also occur in linear homopolymers where they are usually linked internally by α(2,8), α(2,9), or alternating α(2,8)/α(2,9) glycosidic linkages. These polysialic acids play important roles as neural cell adhesion molecules.[4]

While relatively efficient methods have been developed for the introduction of Neu5Acα(2-3)Gal and Neu5Acα-(2-6)Gal glycosidic linkages, the synthesis of oligosaccharides that contain α(2 → 8)-linked fragments is complicated by the low reactivity of the C-8 hydroxyl of Neu5Ac.[5−7] The latter glycosides have been successfully synthesized by indirect chemical approaches whereby modified sialyl donors are employed that have a participating auxiliary at C-3.[8−11] These highly elaborated donors require, however, laborious procedures for their preparation, and after a glycosylation, additional steps are needed for the removal of the auxiliary. Alternative direct glycosylation approaches have been reported, but these lead to either low yielding glycosylations or formation of unnatural β-sialosides or mixtures of anomers.[12−15]

It is obvious that a versatile sialyl donor needs to be developed that gives excellent yields and high α-anomeric selectivities in *direct* glycosylations with a wide range of acceptors of different reactivities.[7] Such a donor would allow efficient synthesis of oligosaccharides of biological or medical importance that contain multiple sialic acids of different linkage type.

Here, we report that the readily available sialyl donor methyl(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-5-trifluoroacetamido-D-*glycero*-β-D-*galacto*-nonulopyranosid)onate (**2a**) gives good yields and excellent α-anomeric selectivities in direct sialylations with a wide variety of glycosyl acceptors ranging from sterically hindered C-8 hydroxyls of a sialic acid and C-3 hydroxyls of galactosides to reactive primary alcohols. The versatility of the donor allowed a highly efficient synthesis of the human melanoma associated antigen GD_3 derivative, which has multiple Neu5Ac residues (Figure 1).

Results and Discussion

The synthesis of the human melanoma associated antigen GD_3 derivative requires the introduction of Neu5Acα(2-8)Neu5Ac and Neu5Acα(2-3)Gal glycosidic linkages. In addition, the anomeric center of a sialyl acceptor needs temporary protection, which required glycosylation with a primary alcohol. Previous syntheses of the carbohydrate part of this biologically important glycosphingolipid could only be achieved by *indirect* sialylation protocols[16−18] or a strategy whereby an α(2-8)-linked fragment was obtained by controlled degradation of colominic acid.[19−21]

It was anticipated that sialyl donor **2a** (Scheme 1), which is protected with a 5-trifluoroacetamido (*N*-TFA)

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(15) Our attempts to synthesize (2-8)-linked dimers by direct sialylation employing conventional glycosyl donors {2-thiomethyl, 2-thiophenyl, 2-xanthate, and 2-phosphite of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-nonulopyranosid-(yl)onate} failed, and only traces of the desired products were obtained.

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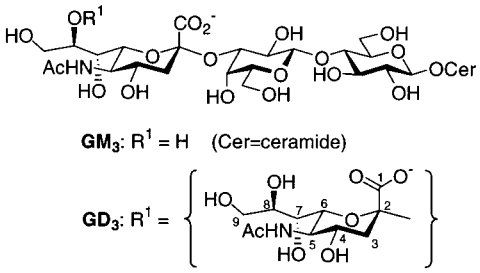
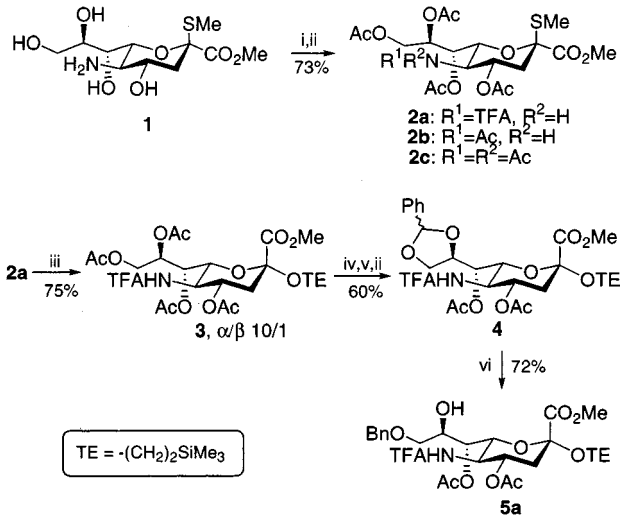


Figure 1.

group, would have superior glycosyl donor properties compared to the traditional donor **2b**,[22] which has an acetamido functionality at C-5, therefore allowing an efficient synthesis of GD_3 by a *direct* sialylation approach. This expectation was based on our recent finding that 2-thio-sialyl donor **2c**, which has an electron-withdrawing *N*-acetylacetamido moiety at C-5, gives significantly higher yields in glycosylations compared to donor **2b**.[14,23] This new glycosyl donor allowed the synthesis of Neu5Acα-(2-8)Neu5Ac dimers in good yields albeit as a mixtures of anomers.[14] The improved glycosyl donor properties of **2c** were rationalized by the fact that protection of the C-5 acetamido group with a strong electron-withdrawing amino protecting group would reduce its nucleophilicity, thereby minimizing possible site reactions in glycosylations. In this respect, it has been observed that the C-5 acetamido group can be glycosylated when unreactive glycosyl acceptors (e.g., C-8 hydroxyl of Neu5Ac) are used.[24]

It was also anticipated that the low reactivity of the C-8 hydroxyl of a neuraminic acid acceptor would be improved when its amino group would be protected as an *N*-TFA derivative. Schmidt and co-worker have proposed that this low reactivity is in part due to unfavorable hydrogen bonding between the C-5-acetamido and C-8 hydroxyl functions.[12,13,25] These unfavorable interactions should be less pronounced when the C-5 amino group is protected as an *N*-TFA function. This predicament is based on studies with *N*-acylated 2-hydroxyanilines wherein it was shown that *N*-trifluoroacetyl derivatives display longer and therefore weaker intermolecular hydrogen bonds (between the C-1 amide and C-2 hydroxyl functions) than do the analogous *N*-benzoylated compounds.[26] An *N*-TFA protecting group has the added advantage that it can be easily introduced and removed under mild reaction conditions. The latter feature makes it feasible to functionalize the amino group of sialic acids as *N*-acetyl, *N*-glycolyl, or other derivatives if desired.

Scheme 1[a]



[a] Reagents and conditions: (i) CF_3COOMe/Et_3N, MeOH; (ii) Ac_2O/pyridine; (iii) $TMS(CH_2)_2OH$, NIS/TfOH/MS3Å, MeCN, −35 °C; (iv) MeONa/MeOH; (v) $(MeO)_2CHPh$/CSA, MeCN; (vi) $BH_3{\cdot}Me_3N/AlCl_3$/MS4Å , THF.

The TFA-protected sialyl donor **2a** and acceptor **5a** were prepared in a highly convergent manner from the known precursor **1**.[27,28] Thus, selective *N*-trifluoracetylation[29] of **1** with CF_3COOMe in the presence of Et_3N in MeOH followed by *O*-acetylation with Ac_2O/pyridine gave sialyl donor **2a** in overall yield of 73%.[30] Compound **1** was readily converted into glycosyl acceptor **5a**. Thus, glycosylation of thioglycoside **2a** with 2-(trimethylsilyl)ethyl alcohol (TEOH) in the presence of NIS/TfOH and molecular sieves in MeCN at −33 °C furnished **3** in a good yield as mainly the α-anomer (75%, $\alpha/\beta = 10/1$). Separation of the anomers could be easily accomplished at a later stage of the synthesis. The glycoside **3** was converted into the selectively protected derivative **4** by subsequent deacetylation with MeONa in MeOH, regioselective protection of the 8,9-diol as a benzylidene acetal by treatment with dimethoxytoluene in the presence of camphorsulfonic acid (CSA) in acetonitrile, and *O*-acetylation of the remaining hydroxyls at C-4 and C-7 with Ac_2O/pyridine. The benzylidene acetal of **4** was regioselectively opened to a C-8 hydroxyl by the treatment with $BH_3{\cdot}NMe_3$ complex[31] in the presence of anhydrous $AlCl_3$ and 4 Å molecular sieves in dry THF to give sialyl acceptor **5a** (Scheme 1).

The glycosyl donor properties of **2a** were examined in glycosylations with the C-8 hydroxyl of sialyl acceptors **5a**−**c** bearing a *N*-TFA, acetamido, or acetylacetamido moiety at C-5, respectively (Scheme 2). Thus, coupling of **2a** with **5a** in the presence of NIS/TfOH/MS3Å in acetonitrile at −35 °C gave (2-8)-linked sialoside **6a** in an excellent yield of 55%. After Sephadex LH-20 size exclusion column chromatography, HPLC and NMR

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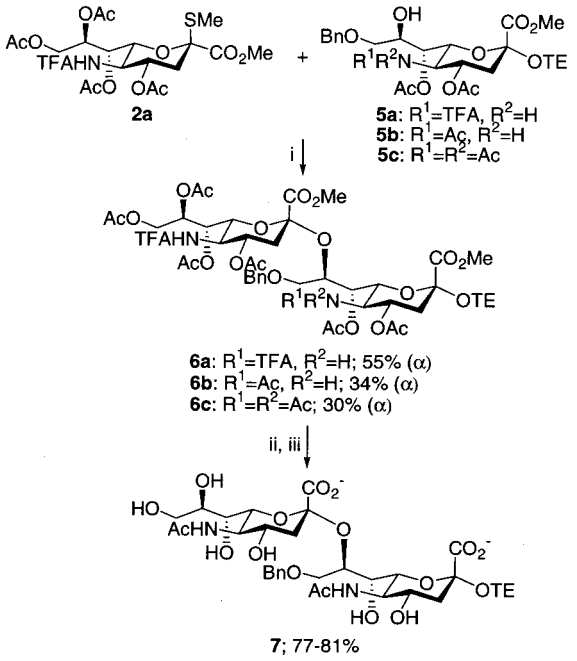
Scheme 2[a]



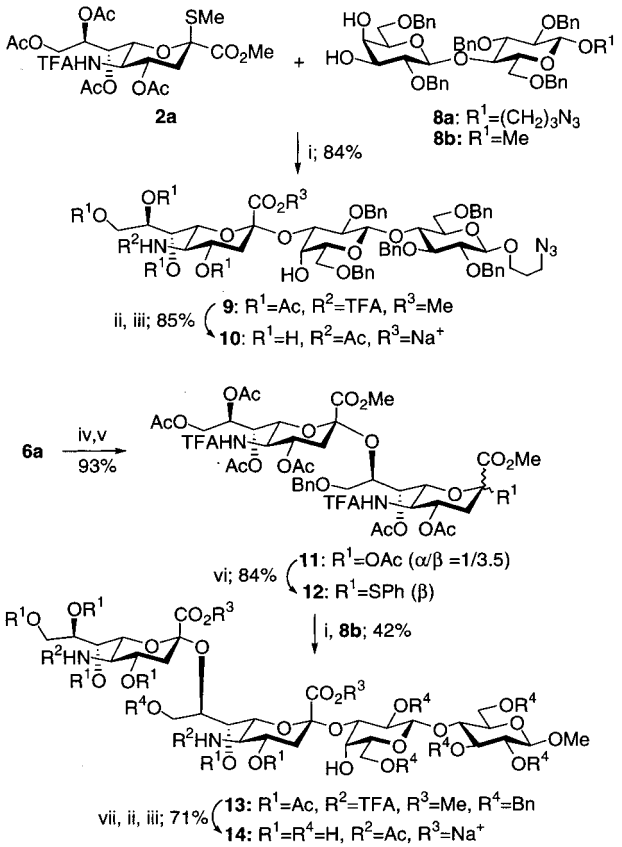
[a] Reagents and conditions: (i) NIS/TfOH/MS3Å, MeCN, 35 °C; (ii) 1 M aq NaOH/MeOH; (iii) Ac_2O/MeOH.

analysis of the product showed the presence of only one anomer. Conventional empirical NMR rules for the assignment of anomeric configurations of sialosides[7] may not be applicable to TFA-protected derivatives. Therefore, dimer **6a** was converted into the known acetamido derivative **7** by concomitant *N*,*O*-deacylation with 1 M aqueous NaOH/MeOH, followed by selective *N*-acetylation with Ac_2O in MeOH. The NMR data and optical rotation of **7** unambiguously confirmed the α-anomeric configuration of the product. Thus, *H*-3′eq in the ^{1}H NMR spectrum of **7** was shifted downfield (δ = 2.60 ppm) compared to that of the previously synthesized β-anomer (δ = 2.37 ppm),[14] whereas *H*-4′ of **7** appeared at higher field (δ = 3.53 ppm) than that of β-anomer (δ = 4.05 ppm).

Glycosylation of 5**b** and **5c**[14] with **2a** under similar reaction conditions (NIS/TfOH/MS3Å/MeCN, −35 °C) provided stereoselective formation of α-sialosides **6b** and **6c**, respectively, but yields were significantly lower (34 and 30% yield, respectively). The modest yield of **6c** could be explained by a competing acetyl group migration from N-5 to N-8 of acceptor **5c,** whereas the nucleophilicity and basicity of the acetamido moiety of **5b** probably caused the low yield of **6b**. It is important to note that glycosylation of **2b**[22] or **2c**[23] with acceptor **5a** gave mixtures of anomers in poor or reasonable yield, respectively, demonstrating the superior glycosyl donating properties of **2a**.

Encouraged by these results, attention was focused on the formation of sialosides of a C-3 hydroxyl of the galactosyl residue of a partially protected derivative of D-lactose (Scheme 3). Thus, NIS/TfOH-mediated coupling of **2a** with partially protected lactosyl acceptor **8a**[32] gave trisaccharide **9** in an excellent yield of 84% as only the α-anomer. This is a remarkable result because similar glycosylations with monosaccharide donor **2b**, which has

Scheme 3[a]



[a] Reagents and conditions: (i) NIS/TfOH/MS3Å , MeCN, 35 °C; (ii) 1 M aq NaOH/MeOH; (iii) Ac_2O/MeOH; (iv) TFA, DCE; (v) Ac_2O/C_6H_5N; (vi) PhSH/BF_3·Et2O/MS3Å , DCM; (vii) H_2, $Pd(OAc)_2$, EtOH/EtOAc, 1/1.

a conventional NHAc at C-5, gave anomeric mixtures with yields ranging from 30% to 60%.[33] Furthermore, these traditional glycosylations require up to 3 equiv of glycosyl donor **2a**, whereas for the preparation of **9** only 2 equiv of **2a** were used. The *N*-TFA protecting group of **9** was converted into the *N*-acetyl derivative by a two-step procedure to give **10** in an 85% overall yield. In this case, the NMR data of **10** also unambiguously confirmed the presence of α-sialyl linkage (H-4" δ = 3.79 ppm, $\Delta\delta$ {H-9"a − H-9"b} = 0.12 ppm).

For the synthesis of GD_3 derivative **14**, dimer **6a** was converted into the second-generation thioglycosyl donor **12** (Scheme 3). Cleavage of the anomeric 2-(trimethylsilyl)ethyl glycoside of **6a** with TFA/DCM, followed by acetylation of the resulting lactol with Ac_2O/pyridine gave anomeric acetate **11** as predominantly the β-anomer. Conversion of the anomeric acetate of **11** into a 2-thiophenyl sialoside **12** was easily accomplished by the treatment with thiophenol in the presence of BF_3·Et_2O. On the other hand, reaction of **11** with TMSSMe was very sluggish and gave the corresponding 2-thiomethyl sialoside in a low yield.[22] NIS/TfOH-mediated glycosylation of **12** with lactosyl acceptor **8b**[34] afforded tetrasaccharide **13** in an excellent yield of 42% as only the α-anomer. In this case, only 1 equiv of sialyl donor **12** was used to achieve this result. Furthermore, the stereoselective preparation of

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disaccharides **6a**−**c**, trisaccharide **9**, and tetrasaccharide **13** indicates that, regardless of the protecting group pattern of donor and acceptor, *N*-TFA-protected sialyl donors give stereoselective formation of α-sialosides in good yields. The benzyl ethers of compound **13** were removed by catalytic hydrogenation over $Pd(OAc)_2$, and the *N*-TFA of the resulting intermediate was converted into the corresponding acetamido moiety by the treatment with sodium hydroxide followed by *N*-acetylation with acetic anhydride in methanol to give the requisite GD_3 derivative **14**. The NMR data of **14** showed that only the required α-linked sialosides were formed. On the basis of the NMR data of **2a**, **6a**−**c**, **9**, and **11**−**13** the anomeric configuration of *N*-TFA-protected derivatives can be determined from the chemical shift data of *H*-4 (δ = 5.30−5.45 ppm for β-anomers and δ = 4.92−5.11 ppm for α-anomers).

Conclusion

It has been shown that modification of the C-5 amino group of 2-methyl and 2-thiophenyl sialosides into *N*-TFA derivatives provides glycosyl donors that give good yields and high α-anomeric selectivities in direct sialylations with a wide range of glycosyl acceptors of differing reactivities. These new donors allowed, for the first time, the stereoselective synthesis of α-(2-8)-linked dimers in high yields. The best yields were obtained when the amino functionality of the sialyl acceptor was also protected as *N*-TFA derivative. The favorable properties of the new donors allowed a highly efficient synthesis of the human melanoma associated antigen GD_3 derivative, which has two Neu5Ac residues of different linkage type. A *N*-TFA-substituted sialyl donor has previously been employed for the preparation of a 6-sulfo-de-*N*-acetylsialyl Le^x ganglioside; however, no improved glycosyl donor properties were reported.[30] The *N*-TFA protecting group could be easily transformed into Neu5Ac derivatives, and potentially they open an efficient route toward sialic acid containing oligosaccharides that have modified amino functionalities. We postulate that the efficiency of the glycosylations results from a lower nucleophilicity of TFA-protected amino functionalities and enhanced reactivity of a C-8 hydroxyl of a sialyl acceptor. The origin of the high α-selectivity of *N*-TFA-protected sialyl donors is still unclear, and further studies are underway to shed light on this effect.

Experimental Section

General. Column chromatography was performed on silica gel 60 (EM Science, 70−230 mesh), size exclusion column chromatography was performed on Sephadex LH-20 (MeOH or MeOH/CH_2Cl_2, 1/1, v/v elution) or Sephadex G-25 (water elution). HPLC chromatography was performed on Prodigy 5 μm silica 100 Å column (250 × 10 mm, CH_2Cl_2/ethyl acetate elution). Reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science), and the compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. CH_2Cl_2, $(ClCH_2)_2$, and MeCN were distilled from CaH_2 (twice) and stored over molecular sieves (3 Å). THF was distilled from sodium directly prior to the application. Methanol was dried by refluxing with magnesium methoxide, distilled, and stored under argon. Pyridine was dried by refluxing with CaH_2, then distilled ,and stored over molecular sieves (3 Å). Molecular sieves (3 and 4 Å) used for reactions were crushed and activated in vacuo at 390 °C during 8 h in the first instance and then for 2−3 h at 390 °C directly prior to application. Optical rotations were measured with a Jasco P-1020 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian Inova500 spectrometer and a Varian Inova600 spectrometer equipped with Sun workstations. Unless otherwise noted ^1H NMR spectra were recorded in $CDCl_3$ and referenced to residual $CHCl_3$ at 7.24 ppm, and ^{13}C NMR spectra to the central peak of $CDCl_3$ at 77.0 ppm. Assignments were made by standard gCOSY and gHSQC. High-resolution mass spectra were run in a JMS SX/SX102A tandem mass spectrometer, equipped with FAB source. The matrix used was thioglycerol, and the internal standards were ultramark 1621 and PEG.

Methyl (Methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-5-trifluoroacetamido-D-*glycero*-β-D-*galacto*-non-2-ulopyranosid)onate (2a). Methyl trifluoroacetate (3.5 mL, 34 mmol) was added to a solution of **1** (1.07 g, 3.44 mmol) and triethylamine (0.96 mL, 6.9 mmol) in methanol (40 mL). After 1.5 h, the reaction mixture was concentrated under reduced pressure and dried in vacuo. Pyridine (20 mL) and Ac_2O (10 mL) were added to the residue. After 16 h, the reaction was quenched with MeOH (15 mL), concentrated, coevaporated with toluene (3 × 15 mL), and dried in vacuo. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in hexane) to afford **2a** as a white foam (1.44 g, 73%): FAB MS *m*/*z* 598.1 $[M + Na]^+$; R_f 0.51 (acetone/toluene, 3/7, v/v); $[\alpha]^{27}_D = -44.4$ (*c* 0.6, $CHCl_3$); ^1H NMR δ 6.77 (d, 1H, $J_{NH,5}$ = 10.1 Hz, NH), 5.37−5.44 (m, 2H, $J_{4,5}$ = 11.5 Hz, $J_{7,8}$ = 11.2 Hz, H-4, 7), 5.16−5.19 (m, 1H, $J_{8,9a}$ = 2.5 Hz, $J_{8,9b}$ = 7.8 Hz, H-8), 4.78 (dd, 1H, $J_{9a,9b}$ = 12.5 Hz, H-9a), 4.50 (dd, 1H, $J_{6,7}$ = 2.5 Hz, H-6), 4.18 (dd, 1H, H-9b), 4.03 (dd, 1H, $J_{5,6}$ = 10.5 Hz, H-5), 3.83 (s, 3H, OCH_3), 2.58 (dd, 1H, $J_{3e,4}$ = 5.0 Hz, $J_{3e,3a}$ = 13.4 Hz, H-3e), 2.16 (dd, 1H, H-3a), 2.14, 2.09, 2.05, 2.04, (4s, 12H, $OCOCH_3$), 2.03 (s, 3H, SMe); ^{13}C NMR δ 171.4, 171.1, 170.6, 170.0, 167.8, 167.7, 85.0, 72.6, 71.3, 68.9, 68.5, 62.5, 53.2, 50.6, 37.2, 21.3, 21.1, 20.9, 11.73; HR-FAB MS $[M + H]^+$ calcd for $C_{21}H_{29}O_{12}NF_3S$ 576.1363, found 576.1360.

Methyl [2-(Trimethylsilyl)ethyl 4,7,9-tri-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α,β-D-*galacto*-non-2-ulopyranosid]onate (3). A mixture of **2a** (1 g, 1.74 mmol), 2-(trimethylsilyl)ethanol (0.5 mL, 3.5 mmol), and activated molecular sieves (3 Å, 300 mg) in MeCN (35 mL) was stirred for 16 h under an atmosphere of argon at room temperature and then cooled to −35 °C, and NIS (783 mg, 3.48 mmol) and TfOH (31 μL, 0.35 mmol) were added. The reaction mixture was stirred for 15 min until TLC analysis indicated that the reaction had gone to completion. The reaction mixture was diluted with DCM (100 mL), the solids were filtered off, and the residue was washed with DCM (3 × 100 mL). The combined filtrate (400 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 150 mL) and H_2O (3 × 80 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in hexane) to afford **3** as 10/1 α/β-mixture (848 mg, 75%) as a white foam. Analytical data for α-**3**: FAB MS *m*/*z* 646.2 $[M + H]^+$; R_f 0.35 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]^{27}_D = -8.3$ (*c* 0.6, $CHCl_3$); ^1H NMR δ 6.24 (d, 1H, $J_{NH,5}$ = 9.8 Hz, NH), 5.35−5.40 (m, 1H, $J_{8,9a}$ = 2.4 Hz, $J_{8,9b}$ = 4.9 Hz, H-8), 5.26 (dd, 1H, $J_{7,8}$ = 8.3 Hz, H-7), 4.92−4.98 (m, 1H, $J_{4,5}$ = 10.2 Hz, H-4) 4.27 (dd, 1H, $J_{9a,9b}$ = 12.7 Hz, H-9a), 4.23 (dd, 1H, $J_{6,7}$ = 1.9 Hz, H-6), 4.11 (dd, 1H, H-9b), 3.94 (dd, 1H, $J_{5,6}$ = 10.7 Hz, H-5), 3.84−3.90 (m, 1H, J^2= 9.3 Hz, OCH_2a) 3.79 (s, 3H, OCH_3), 3.28−3.34 (m, 1H, OCH_2b), 2.62 (dd, 1H, $J_{3e,4}$ = 4.4 Hz, $J_{3e,3a}$ = 12.7 Hz, H-3e), 2.14, 2.11, 2.01, 1.99, (4s, 12H, $OCOCH_3$), 1.90 (t, 1H, H-3a), 0.80−0.92 (m, 2H, CH_2TMS), 0.00 (s, 9H, TMS); ^{13}C NMR δ 71.5, 67.0, 62.8, 62.7, 62.0, 52.6, 50.4, 38.3, 20.8, 20.5, 20.4, 17.9, 10.9; HR-FAB MS $[M + H]^+$ calcd for $C_{25}H_{39}O_{13}NF_3Si$ 646.2143, found 646.2148.

Methyl [2-(Trimethylsilyl)ethyl 4,7-di-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (5a). Sodium methoxide (7 mL, 1 M solution in methanol) was added to the solution of **3** (848 mg, 1.31 mmol) in methanol (100 mL). After 2 h, the

reaction mixture was neutralized with Dowex-50 H^+ resin (pH = 7), which was removed by filtration. The filtrate was concentrated under reduced pressure to afford methyl [2-(trimethylsilyl)ethyl 3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (615 mg, 98%). The residue was dissolved in MeCN (15 mL), and benzaldehyde dimethyl acetal (0.39 mL, 2.57 mmol) and CSA (30 mg, 0.13 mmol) were added. After 1 h, the reaction mixture was neutralized with triethylamine (pH = 7), and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (70 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and H_2O (3 × 25 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in toluene) to afford anomerically pure methyl [2-(trimethylsilyl)ethyl 8,9-*O*-benzylidene-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate as a white foam (447 mg, 61%, *exo*/*endo* 1/1), which was dissolved in a mixture of Ac_2O (8 mL) and pyridine (16 mL). After 16 h, the reaction was quenched with MeOH (10 mL) and concentrated in vacuo, and the residue was coevaporated with toluene (3 × 20 mL) to give **4** as a white foam (492 mg, 96%), which was used without further purification; R_f 0.42 (acetone/hexane, 2/3 v/v). Comparison of the integral intensities of NH 6.31 (d, 1H) and 6.20 (d, 1H), or C*H*Ph 5.87 (s, 1H) and 5.79 (s, 1H) signals in the ^{1}H NMR spectrum showed 1:1 mixture of *exo*/*endo* isomers. BH_3·NMe_3 (307 mg, 4.21 mmol) and $AlCl_3$ (546 mg, 4.10 mmol) were added to a solution of **4** (441 mg, 0.68 mmol) and activated molecular sieves (4 Å, 2.65 g) in THF (8 mL) at 0 °C. After stirring for 2 h at 0 °C and another 3 h at room temperature, the reaction mixture was diluted with Et_2O (50 mL), and the solids were filtered off and washed with Et_2O (3 × 50 mL). The combined filtrate (200 mL) was washed with saturated aqueous $NaHCO_3$ (2 × 70 mL) and H_2O (3 × 40 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient ethyl acetate in toluene) to afford **5a** as a white foam (319 mg, 72%): FAB MS *m*/*z* 652.2 $[M + H]^+$; R_f 0.55 (ethyl acetate/toluene 2/3, v/v); $[\alpha]^{27}_D = -4.7$ (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.20−7.37 (m, 5H, aromatic), 6.54 (d, 1H, $J_{NH,5}$ =7.8 Hz, NH), 5.12 (d, 1H, $J_{7,8}$ = 8.8 Hz, H-7) 4.92−5.00 (m, 1H, $J_{4,5}$ = 9.8 Hz H-4), 4.50−4.58 (m, 2H, CH_2Ph), 4.11−4.17 (m, 1H, $J_{8,9a}$ = 3.4 Hz, $J_{8,9b}$ = 6.0 Hz, H-8), 4.05−4.10 (m, 2H, H-5, 6), 3.89 (dd, 1H, J^2 = 8.5 Hz, OCH_2a), 3.86 (s, 3H, OCH_3), 3.76 (d, 1H, $J_{OH,8}$ = 6.0 Hz, OH), 3.53 (dd, 1H, $J_{9a,9b}$ = 10.2 Hz, H-9a), 3.46 (dd, 1H, H-9b), 3.42 (dd, 1H, OCH_2b), 2.73 (dd, 1H, $J_{3e,4}$ = 4.9 Hz, $J_{3e,3a}$ = 12.7 Hz, H-3e), 2.09, 2.02, (2s, 6H, OCOCH_3) 1.98 (t, 1H, H-3a), 0−84−0.95 (m, 2H, CH_2TMS), 0.00 (s, 3H, TMS); ^{13}C NMR δ 170.8, 170.2, 169.5, 158.0, 138.0, 128.5, 128.2, 127.8, 98.8, 73.8, 72.2, 70.9, 69.6, 69.2, 62.77, 53.7, 50.3, 37.9, 21.1, 20.9, 18.3, −0.93; HR-FAB MS $[M + H]^+$ calcd for $C_{28}H_{41}O_{11}NF_3Si$ 652.2401, found 652.2410.

Methyl [2-(Trimethylsilyl)ethyl 4,7-di-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-8-*O*-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (6a). A mixture of donor **2a** (85 mg, 0.147 mmol), **5a** (32 mg, 0.049 mmol), and activated molecular sieves (3 Å, 250 mg) in MeCN (1.5 mL) was stirred for 16 h under an atmosphere of argon at room temperature. The mixture was cooled to −35 °C, NIS (0.294 mmol) and TfOH (0.03 mmol) were added, and the reaction mixture was stirred for 5 min until TLC analysis indicated that reaction had gone to completion. The reaction mixture was diluted with DCM (10 mL), the solids were filtered off, and the residue was washed with DCM (3 × 10 mL). The combined filtrate (40 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 15 mL) and H_2O (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by size exclusion column chromatography on Sephadex LH-20 (methanol/dichloromethane, 1/1, v/v) to afford **6a** as a white foam (32.0 mg, 55%): FAB MS *m*/*z* 1201.3 $[M + Na]^+$; R_f 0.51 (ethyl acetate/hexane, 5/5, v/v); $[\alpha]^{27}_D = +2.7$ (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.67 (d, 1H, $J_{NH,5}$ = 9.8 Hz, NH), 7.25−7.37 (m, 5H, aromatic), 6.24 (d, 1H, $J_{NH,5'}$ = 9.3 Hz, NH), 5.58−5.62 (m, 1H, $J_{8',9'b}$ = 1.9 Hz, H-8′), 5.32 (dd, 1H, $J_{7',8'}$ = 9.8 Hz, H-7′), 5.23 (d, 1H, H-7), 5.17 (d, 1H, $J_{8,9b}$ = 7.8 Hz, H-8), 4.99−5.06 (m, 1H, $J_{4',5'}$ = 9.8 Hz, H-4′), 4.89−4.96 (m, 1H, $J_{4,5}$ = 11.7 Hz, H-4), 4.56 (dd, 2H, J^2 = 11.7 Hz, CH_2Ph), 4.42 (dd, 1H, $J_{6,7}$ = 2.4 Hz, H-6), 4.38 (dd, 1H, $J_{9'a\ 9'b}$ = 12.7 Hz, H-9′a), 4.21 (dd, 1H, H-9′b), 4.07−3.95 (m, 3H, $J_{5,6}$ = 10.2 Hz, $J_{6',7'}$ = 1.5 Hz, $J_{9a,9b}$ = 11.2 Hz, H-5, 5′, 6′, 9a), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.81 (m, 1H, J^2 = 8.8 Hz, OCH_2a), 3.54 (dd, 1H, H-9b), 3.31−3.37 (m, 1H, OCH_2b), 2.78 (dd,1H, $J_{3'e,4'}$ = 4.4 Hz, $J_{3'e,3'a}$ = 12.7 Hz, H-3′e), 2.72 (dd,1H, $J_{3e,4}$ = 4.9 Hz, $J_{3e,3a}$ = 12.7 Hz, H-3e), 2.20, 2.06, 2.05, 2.02, 2.01, 2.00 (6s, 18H, OCOCH_3), 2.07−2.18 (m, 1H, H-3′a), 1.93 (dd, 1H, H-3a), 0.75−0.90 (m, 2H, CH_2TMS), −0.01 (s, 3H, TMS); ^{13}C NMR δ 172.3, 171.2, 170.8, 170.3, 169.9, 169.8, 168.9, 168.4, 157.6, 138.9, 128.5, 127.6, 127.4, 99.01, 96.9, 73.9, 73.8, 72.5, 71.8, 10.6, 69.9, 69.4, 68.7, 68.6, 66.9, 62.7, 62.5, 53.6, 52.9, 50.8, 50.0, 38.9, 38.2, 31.2, 30.0, 21.5, 20.9, 20.8, 20.7, 18.2, −0.92; HR-FAB MS $[M + Na]^+$ calcd for $C_{48}H_{64}O_{23}N_2F_6NaSi$ 1201.3471, found 1201.3472.

Methyl [2-(Trimethylsilyl)ethyl 5-acetamido-4,7-di-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-8-*O*-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (6b). A mixture of donor **2a** (81 mg, 0.140 mmol), **5b** (28 mg, 0.047 mmol), and activated molecular sieves (3 Å, 300 mg) in MeCN (0.5 mL) was stirred for 16 h under an atmosphere of argon. The mixture was cooled to −35 °C, NIS (0.28 mmol) and TfOH (0.03 mmol) were added, and the reaction mixture was stirred for 20 min until TLC analysis indicated that reaction had gone to completion. The reaction mixture was diluted with DCM (10 mL), the solids were filtered off, and the residue was washed with DCM (3 × 10 mL). The combined filtrate (40 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 15 mL) and H_2O (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by size exclusion column chromatography on Sephadex LH-20 (methanol/dichloromethane, 1/1, v/v) to afford **6b** as a white foam (18.0 mg, 34%): FAB MS *m*/*z* 1125.4 $[M + H]^+$; R_f 0.51 (acetone/toluene, 5/5, v/v); $[\alpha]^{27}_D = +2.4$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.31−7.37 (m, 5H, aromatic), 6.37 (d, 1H, $J_{NH,5}$ = 9.6 Hz, NH), 6.17 (d, 1H, $J_{NH,5'}$ = 9.9 Hz, NH), 5.51−5.56 (m, 1H, $J_{8',9'}$ = 4.3 Hz, H-8′), 5.29 (dd, 1H, $J_{7',8'}$ = 9.8 Hz, H-7′), 5.24 (bs, 1H, H-7), 5.00−5.07 (m, 2H, $J_{4',5'}$ = 10.2 Hz, $J_{8,9b}$ = 8.9 Hz, H-4′, 8), 4.86−4.92 (m, 1H, $J_{4,5}$ = 11.7 Hz, H-4), 4.71 (dd, 2H, J^2 =11.6 Hz, CH_2Ph), 4.25−4.30 (m, 2H, $J_{9'a,9'b}$ = 12.7 Hz, H-9′) 4.17 (dd, 1H, $J_{6,7}$ =1.9 Hz, H-6), 4.02−4.08 (m, 2H, $J_{6',7'}$ = 1.4 Hz, $J_{9a,9b}$ = 11.9 Hz, H-6′, 9a), 3.93−4.02 (m, 2H, $J_{5',6'}$ = 9.7 Hz, $J_{5,6}$ = 10.6 Hz, H-5′, 5), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.78−3.84 (m, 1H, J^2 =9.3 Hz, OCH_2a), 3.55 (dd, 1H, H-9b), 3.34−3.40 (m, 1H, OC$H_{2b)}$, 2.76 (dd, 1H, $J_{3'e,4'}$ = 4.7 Hz, $J_{3'e,3'a}$ = 12.9 Hz, H-3′e), 2.65 (dd, 1H, $J_{3e,4}$ = 4.8 Hz, $J_{3e,3a}$ = 12.8 Hz, H-3e), 2.22 (s, 3H, NHCOCH_3), 2.06, 2.05, 2.04, 2.02, 2.01, 1.90 (6s, 18H, OCOCH_3), 2.03 (m, 1H, H-3′a), 1.91 (dd, 1H, H-3a), 0.76−0.90 (m, 2H, CH_2TMS), 0.00 (s, 3H, TMS); ^{13}C NMR δ 171.3, 171.1, 170.8, 170.6, 170.2, 170.0, 168.7, 168.5, 138.9, 128.5, 127.6, 127.4, 99.0, 97.4, 74.4, 74.0, 72.7, 71.7, 70.5, 70.0, 68.6, 67.1, 62.6, 62.4, 53.5, 52.8, 50.9, 49.3, 38.7, 38.1, 30.0, 23.4, 21.8, 21.3, 21.1, 21.0, 18.3, −0.89; HR-FAB MS $[M + H]^+$ calcd for $C_{48}H_{68}O_{23}N_2F_3NaSi$ 1125.3934, found 1125.3900.

Methyl [2-(Trimethylsilyl)ethyl 5-(*N*-acetylacetamido)-4,7-di-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-8-*O*-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (6c). A mixture of donor **2a** (97 mg, 0.169 mmol), **5c** (36 mg, 0.056 mmol), and activated molecular sieves (3 Å, 340 mg) in MeCN (2.0 mL) was stirred for 16 h under an atmosphere of argon. The mixture was cooled to −35 °C, NIS (0.34 mmol) and TfOH (0.03 mmol) were added, and the reaction mixture was stirred for 5 min until TLC analysis indicated that reaction had gone to completion. The

reaction mixture was diluted with DCM (10 mL), the solids were filtered off, and the residue was washed with DCM (3 × 10 mL). The combined filtrate (40 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 15 mL) and H_2O (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by size exclusion column chromatography on Sephadex LH-20 (methanol/dichloromethane, 1/1, v/v) to afford **6c** as a white foam (19.5 mg, 30%): FAB MS *m/z* 1189.4 $[M + Na]^+$; R_f 0.53 (ethyl acetate/ hexane, 5/5, v/v); $[\alpha]^{27}_D = -6.2$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.23−7.39 (m, 5H, aromatic), 6.21 (d, 1H, $J_{NH,5'} = 9.6$ Hz, NH), 5.49−5.56 (m, 1H, $J_{4,5} = 10.4$ Hz, H-4), 5.29−5.33 (m, 1H, $J_{8',9'a} = 2.4$ Hz, $J_{8',9'b} = 3.7$ Hz, H-8′), 5.26 (dd, 1H, $J_{7',8'} = 9.2$ Hz, H-7′), 5.04−5.11 (m, 2H, $J_{4',5'} = 10.4$ Hz, $J_{7,8} = 9.2$ Hz, H-4′, 7), 4.96 (dd, 1H, $J_{6,7} = 1.4$ Hz, H-6), 4.59 (dd, 2H, $J^2 = 12.0$ Hz, CH_2Ph.), 4.41−4.45 (m, 1H, $J_{8,9a} = 4.3$ Hz, $J_{8,9b} = 6.4$ Hz, H-8), 4.24 (dd, 1H, $J_{9'a,9'b} = 12.6$ Hz, H-9′a), 4.03−4.12 (m, 4H, $J_{5,6} = 9.9$ Hz, $J_{6',7'} = 1.8$ Hz, $J_{9a,9b} = 11.2$ Hz H-5, 6′, 9a, 9′b), 3.89 (m, 1H, $J_{5',6'} = 9.9$ Hz, H-5′), 3.87 (m, 1H, $J^2 = 8.8$ Hz, OCH_2a), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.68 (dd, 1H, H-9b), 3.34 (m, 1H, OCH_2b), 2.75 (dd,1H, $J_{3e,4} = 5.5$ Hz, $J_{3e,3a} = 13$ Hz, H-3e), 2.67 (dd,1H, $J_{3'e,4'} = 4.8$ Hz, $J_{3'e,3'a} = 13$ Hz, H-3′e), 2.30, 2.28 (2s, 6H, N(COCH_3)$_2$), 2.16, 2.03, 2.01, 1.99, 1.98, (5s, 18H, OCOCH_3), 2.01 (m, 1H, H-3′a), 1.84 (dd, 1H, H-3a), 0.84−0.88 (m, 2H, CH_2TMS), 0.00 (s, 3H, TMS); ^{13}C NMR δ 174.2, 174.0, 170.7, 170.2, 170.1, 169.7, 169.6, 168.2, 168.1, 157.4, 139.0, 128.3, 127.6, 127.4, 99.4, 98.9, 75.3, 73.6, 71.7, 71.1, 70.8, 70.3, 68.7, 68.4, 67.1, 66.9, 62.4, 62.1, 60.7, 57.9, 53.4, 52.9, 50.7, 39.1, 38.5, 30.0, 28.2, 26.1, 21.4, 21.3, 21.1, 21.0, 20.9, 18.4, 14.6, −0.88; HR-FAB MS $[M + Na]^+$ calcd for $C_{50}H_{69}O_{24}N_2F_3NaSi$ 1189.3859, found 1189.3880.

2-(Trimethylsilyl)ethyl 5-Acetamido-8-*O*-(5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-9-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosonic Acid Disodium Salt (7). From 6a. Aqueous NaOH (1 M, 0.5 mL) was added dropwise to a solution of **6a** (20 mg, 16.9 μmol) in MeOH (1 mL). After 72 h (control TLC, methanol/*n*-buthanol/water/triethylamine, 20/60/15/5, v/v/v/v) the reaction mixture was concentrated in vacuo, and the residue was subjected to freeze-drying for 16 h. MeOH (0.8 mL) and Ac_2O (0.2 mL) were added, and the reaction mixture was kept for 16 h and then concentrated under the reduced pressure. The residue was purified by size exclusion column chromatography on Sephadex G25 (35 cm^3, water elution) to afford **7** (11 mg, 78%) as a white film: FAB MS *m/z* 857.3 $[M + H]^+$; R_f 0.42; $[\alpha]^{27}_D = +7.8$ (*c* 0.375, H_2O); ^{1}H NMR (D_2O) δ 7.21−7.30 (m, 5H, arom), 4.51 (dd, 2H, $J^2 = 11.8$ Hz, CH_2Ph), 4.35−4.38 (m, 1H, $J_{8',9'a} = 2.4$ Hz, H-8′), 4.11 (dd, 1H, $J_{9'a,9'b} = 11.7$ Hz, H-9′a), 3.64−3.80 (m, 8H, $J_{7',8'} = 7.8$ Hz, H-5, 6, 5′, 6′, 7′, 9a, 9′b, OCH_2a), 3.50−3.58 (m, 2H, H-4′, 8), 3.35−3.47 (m, 4H, H-4, 7, 9b, OCH_2b), 2.60 (dd, 1H, $J_{3'e,3'a} = 12.6$ Hz, $J_{3'e,4'} = 4.7$, H-3′e), 2.49 (dd, 1H, $J_{3e,3a} = 12.6$ Hz, $J_{3e,4} = 4.1$, H-3e), 1.92, 1.88 (2s, 6H, NHCOCH_3) 1.60 (t, 1H, H-3′a), 1.41 (dd, 1H, H-3a), 0.67−0.77 (m, 2H, CH_2TMS), −0.18 (s, 3H, TMS); ^{13}C NMR (D_2O) δ 175.2, 173.9, 173.5, 137.8, 128.8, 128.3, 101.3, 100.4, 76.1, 74.4, 73.4, 72.7, 72.2, 71.8, 71.0, 70.2, 68.8, 68.4, 68.2, 63.2, 62.7, 52.7, 51.9, 41.2, 40.6, 22.5, 22.2, 18.0, −3.0. The compound **7** obtained from **6b**, **6c**, and isolated in a similar way was completely identical (comparison of the NMR data, HPLC retention times, and $[\alpha]_D$ values) to the sample obtained from **6a**.

3-Azidopropyl *O*-[Methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate]-(2 → 3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (9). A mixture of donor **2a** (70 mg, 0.122 mmol), **8a** (53 mg, 0.060 mmol), and activated molecular sieves (3 Å, 320 mg) in MeCN (1.0 mL) was stirred for 16 h under an atmosphere of argon. The mixture was cooled to −35 °C, NIS (0.24 mmol) and TfOH (0.02 mmol) were added, and the reaction mixture was stirred for 5 min until TLC analysis indicated that reaction had gone to completion. The reaction mixture was diluted with DCM (10 mL), the solids were filtered off, and the residue was washed with DCM (3 × 10 mL). The combined filtrate (40 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 15 mL) and H_2O (3 × 20 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by size exclusion column chromatography on Sephadex LH-20 (methanol/dichloromethane, 1/1, v/v) to afford **9** as a white foam (71 mg, 84%): FAB MS *m/z* 1425.5 $[M + Na]^+$; R_f 0.51 (acetone/toluene, 3/7, v/v); $[\alpha]^{27}_D = +3.7$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.20−7.42 (m, 25H, aromatic), 6.28 (d, 1H, $J_{NH,5''} = 9.8$ Hz, NH), 5.44−5.50 (m, 1H, $J_{8'',9''a} = 2.4$ Hz, $J_{8'',9''b} = 5.4$ Hz, H-8″), 5.28 (dd, 1H, $J_{7'',8''} = 8.3$ Hz, H-7″), 4.95−5.01 (m, 1H, $J_{4'',5''} = 10.2$ Hz, H-4″), 4.86 (dd, 2H, $J^2 = 10.7$ Hz, CH_2Ph), 4.77 (dd, 2H, $J^2 = 11.2$ Hz, CH_2Ph), 4.73 (dd, 2H, $J^2 = 11.7$ Hz, CH_2Ph), 4.59 (d, 1H, $J_{1',2'} = 7.3$ Hz, H-1′), 4.49 (dd, 2H, $J^2 = 12.2$ Hz, CH_2Ph), 4.40 (dd, 2H, $J^2 = 11.7$ Hz, CH_2Ph), 4.34 (d, 1H, $J_{1,2} = 7.8$, H-1), 4.27 (dd, 1H, $J_{9''a,9''b} = 12.2$ Hz, H-9″a), 4.17 (dd, 1H, $J_{6'',7''} = 2.0$ Hz, H-6″, 4.05 (dd, 1H, $J_{3',4'} = 3.4$ Hz, H-3′), 3.90−4.03 (m, 4H, H-4, 5″, 9″b, OCH_2a), 3.81 (bt, 1H, H-4′), 3.77 (s, 3H, OCH_3), 3.73, (d, 2H, H-6), 3.67 (dd, 1H, $J_{6'a,6'b} = 11.2$ Hz, H-6′a), 3.58−3.62 (m, 2H, H-3, OCH_2b), 3.46−3.57 (m, 3H, $J_{2',3'} = 9.3$ Hz, $J_{5',6'a} = 8.8$ Hz, H-2′, 5′, 6′b), 3.34−3.41 (m, 4H, $J_{5,6} = 2.9$ Hz, H-2, 5, CH_2N), 2.70 (d, 1H, $J_{OH,4'} = 3.4$ Hz, OH), 2.56 (dd, 1H, $J_{3''e,3''a} = 13.1$ Hz, $J_{3''e,4''} = 4.8$ Hz, H-3″e), 2.01 (m, 1H, 3″a), 2.10, 2.01, 1.98, 1.89 (4s, 12H, OCOCH_3), 1.87 (m, 2H, CCH_2C); ^{13}C NMR δ 170.8, 170.7, 170.3, 169.8, 168.2, 158.0, 157.5, 139.2, 139.0, 138.7, 138.6, 138.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 103.1, 102.5 83.2, 82.1, 78.7, 76.7, 75.6, 75.4, 75.3, 73.6, 73.4, 72.7, 72.2, 69.3, 68.8, 68.7, 68.2, 67.3, 66.7, 62.4, 53.4, 50.3, 48.7, 36.7, 29.6, 21.4, 21.3, 21.0, 20.7; HR-FAB MS $[M + Na]^+$ calcd for $C_{70}H_{81}O_{23}N_4F_3Na$ 1425.5141, found 1425.5109.

3-Azidopropyl *O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-(2 → 3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside Sodium Salt (10). Aqueous NaOH (1 M,0.4 mL) was added dropwise to a solution of **9** (6 mg, 4.27 μmol) in MeOH (1 mL). After 5 h (control TLC, methanol/*n*-buthanol/water/triethylamine, 20/60/15/5, v/v/v/v) the reaction mixture was concentrated in vacuo, and the residue was subjected to freeze-drying for 16 h. MeOH (0.6 mL) and Ac_2O (0.2 mL) were added, and the reaction mixture was kept for 16 h and then concentrated under the reduced pressure. After purification by size exclusion column chromatography on Sephadex LH-20 (35 cm^3, MeOH elution) compound **10** was isolated as a white foam (4.3 mg, 85%): FAB MS *m/z* 1211.6 $[M + Na]^+$; R_f 0.70; ^{1}H NMR (CD_3OD) δ 7.60−7.20 (m, 25H, aromatic), 4.86 (dd, 2H, $J^2 = 10.7$ Hz, CH_2Ph), 4.79 (dd, 2H, $J^2 = 11.2$ Hz, CH_2Ph), 4.72 (dd, 2H, $J^2 = 11.7$ Hz, CH_2Ph), 4.48 (d, 1H, $J_{1',2'} = 7.8$, H-1′), 4.42 (dd, 2H, $J^2 = 11.7$ Hz, CH_2Ph), 4.38 (dd, 2H, $J^2 = 11.7$ Hz, CH_2Ph), 4.37 (d, 1H, $J_{1,2} = 7.8$, H-1), 4.15 (dd, 1H, $J_{3',4'} = 3.3$ Hz, H-3′), 4.01 (d, 1H, H-4′), 3.93−3.98 (m, 1H, $J_{8'',9''} = 2.8$ Hz, $J_{8'',9''b} = 5.0$ Hz, H-8″), 3.88−3.92 (m, 2H, $J_{4,5} = 1.9$ Hz, H-4, OCH_2a), 3.83 (dd, 1H, $J_{6a,6b} = 11.2$ Hz, H-6a), 3.79−3.81 (m, 2H, H-4″, 5″), 3.74 (dd, 1H, $J_{9''a,9''b} = 11.2$ Hz, H-9″a), 3.46−3.68 (m, 10H, $J_{7'',8''} = 8.7$ Hz, H-6′a, 9″b, 6b, 6′b, 2′, 3, 7″, 5′, 6″,OCH_2 b), 3.38 (t, 2H, CH_2N), 3.34 (dd, 1H, $J_{5,6a} = 4.2$ Hz, H-5), 3.25 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-2), 2.86 (dd, 1H, $J_{3''e,3''a} = 12.6$, $J_{3''e,4''} = 4.4$ Hz, H-3″e), 2.02 (s,3H, NHCOCH_3), 1.84 (dd, 1H, $J_{3''a,4''} = 4.1$ Hz, H-3″a), 1.83 (m, 2H, CCH_2C); ^{13}C NMR (CD_3OD) δ 191.4, 178.5, 174.2, 139.3, 138.8, 138.5, 138.3, 128.4, 128.2, 128.0, 127.9, 127.7, 127.5, 127.0, 103.4, 102.8, 82.8, 81.8, 78.6, 76.7, 76.0, 75.3, 75.1, 74.9, 74.8, 74.0, 73.8, 73.2, 73.0, 71.8, 69.8, 68.8, 68.7, 68.1, 66.5, 63.4, 53.0, 48.5, 40.3, 29.7, 21.5; HR-FAB MS $[M + Na]^+$ calcd for $C_{61}H_{73}O_{19}N_4Na_2$ 1211.4664, found 1211.4636.

Methyl [2,4,7-Tri-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-8-*O*-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (11). Trifluoroacetic acid (3 mL) was added dropwise to a solution of **6a** (210 mg, 0.18 mmol) in 1,2-dichloroethane (6 mL). After 2 h, the reaction mixture was concentrated under reduced pressure and dried in vacuo.

Pyridine (6 mL), Ac_2O (3 mL), and DMAP (catalytic amount) were added to the residue. The reaction mixture was kept for 3 days at room temperature, then quenched with MeOH (6 mL), and concentrated in vacuo. The residue was coevaporated with toluene (3 × 6 mL) and dried in vacuo to give **11** as 1/3.5 α/β-mixture (186 mg, 93%) as a white foam, which was separated by silica gel column chromatography (10% gradient ethyl acetate in hexane). Selected analytical data for α-**11**: FAB MS *m*/*z* 1143.3 $[M + Na]^+$; R_f 0.35 (ethyl acetate/hexane 3/2, v/v); $[\alpha]^{25}_D = +3.0$ (*c* 0.6, $CHCl_3$);^{1}H NMR δ 7.95 (d, 1H, $J_{NH,5}$ = 10.2 Hz, NH), 7.25−7.42 (m, 5H, aromatic), 6.23 (d, 1H, $J_{NH,5'}$ = 9.8 Hz, NH), 5.67−5.71 (m, 1H,, $J_{8',9'a}$ = 2.5 Hz H-8′), 5.31 (dd, 1H, $J_{7',8'}$ = 9.1 Hz, H-7′), 5.24 (bs, 1H, H-7), 5.00−5.12 (m, 3H, $J_{8,9b}$ = 8.9 Hz, $J_{4',5'}$ = 9.7 Hz, H-4, 4′, 8), 4.51 (dd, 2H, J^2 = 11.7 Hz, CH_2Ph), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.54 (dd, 1H, $J_{9a,9b}$ = 11.6 Hz, H-9b), 2.78 (dd,1H, $J_{3'e,4'}$ = 4.8 Hz, $J_{3'e,3a'}$ = 12.9 Hz, H-3′e), 2.65 (dd,1H, $J_{3e,\ 4}$ = 5.0 Hz, $J_{3e,\ 3a}$ = 13.6 Hz, H-3e), 2.20, 2.10, 2.06, 2.05, 2.02, 2.01, 1.94 (7s, 21H, OCOCH_3), 2.11−2.21 (m, 1H, H-3′a), 1.98−2.04 (dd, 1H, H-3a).

Analytical data for β-**11**: R_f 0.31 (ethyl acetate/hexane 3/2, v/v); $[\alpha]^{25}_D = -5.0$ (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 7.29−7.40 (m, 6H, NH, aromatic), 6.30 (d, 1H, $J_{NH,5'}$ = 9.2 Hz, NH), 5.34−5.40 (m, 2H,, $J_{8',9'a}$ = 2.5 Hz H-8′, 4), 5.22 (dd, 1H, $J_{7',8'}$ = 9.1 Hz, H-7′), 5.20 (bs, 1H, H-7), 4.96−5.02 (m, 1H, $J_{4',5'}$ = 9.7 Hz, H-4′), 4.59−4.64 (m, 1H, $J_{8,9b}$ = 7.9 Hz, H-8), 4.53 (dd, 2H, J^2 = 12.1 Hz, CH_2Ph), 4.33 (dd, 1H, $J_{6,7}$ = 2.2 Hz, H-6), 4.25 (dd, 1H, $J_{9'a\ 9'b}$ = 12.4 Hz, H-9′a), 3.89−4.07 (m, 5H, $J_{5,6}$ = 10.9 Hz, $J_{6',7'}$ = 1.6 Hz, $J_{9a,9b}$ = 11.5 Hz, H-5, 5′, 6′, 9a,9′b), 3.79 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.56 (dd, 1H, H-9b), 2.69 (dd,1H, $J_{3'e,4'}$ = 4.4 Hz, $J_{3'e,3a'}$ = 13.0 Hz, H-3′e), 2.57 (dd,1H, $J_{3e,\ 4}$ = 5.1 Hz, $J_{3e,\ 3a}$ = 13.5 Hz, H-3e), 2.18, 2.16, 2.03, 2.02, 1.98, 1.97, 1.96 (7s, 21H, OCOCH_3), 1.94−2.00 (m, 2H, H-3′a, 3a); ^{13}C NMR δ 172.3, 171.2, 170.8, 170.3, 169.9, 169.8, 168.9, 168.4, 157.4, 138.9, 128.5, 127.6, 127.4, 99.01, 96.9, 73.9, 73.8, 72.5, 71.8, 70.6, 69.9, 69.4, 68.7, 68.6, 66.9, 62.7, 62.5, 53.6, 52.9, 50.8, 50.0, 38.9, 38.2, 31.2, 30.0, 21.5, 20.9, 20.8, 20.7, 18.2, −0.92

Methyl [Phenyl 4,7-tri-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-8-*O*-(methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-2-thio-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid]onate (12). To a solution of **11** (82.5 mg, 0.07 mmol) in 1,2-dichloroethane (1 mL) were added benzenethiol (30 μL, 0.3 mmol) and BF_3·Et_2O (37 mL, 0.3 mmol). After 30 min, the reaction mixture was diluted with DCM (6 mL) and then washed with aqueous $NaHCO_3$ (15%, 2 mL) and H_2O (3 × 6 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% gradient acetone in toluene) to afford anomerically pure **12** as white foam (72 mg, 84%): FAB MS *m*/*z* 1172.0 $[M + H]^+$; R_f 0.60 (acetone/toluene 3/7, v/v); $[\alpha]^{25}_D = +5.7$ (*c* 0.1, $CHCl_3$); ^{1}H NMR δ 8.03 (d, 1H, $J_{NH,5}$ = 10.5 Hz, NH), 7.18−7.54 (m, 10H, aromatic), 6.16 (d, 1H, $J_{NH,5'}$ = 9.4 Hz, NH), 5.60−5.66 (m, 1H, $J_{8',9'a}$ = 2.3 Hz, $J_{8',9'b}$ = 4.9 Hz, H-8′), 5.33−5.40 (m, 2H, H-4, 7), 5.27 (d, 1H, $J_{7',8'}$ = 10.0 Hz, H-7′), 5.09 (dd, 1H, $J_{6,7}$ = 1.8 Hz, H-6), 4.99−5.06 (m, 1H, H-4′,8), 4.49 (dd, 2H, J^2 = 12.2 Hz, CH_2Ph), 4.15 (dd, 1H, $J_{9'a\ 9'b}$ = 12.6 Hz, H-9′a), 4.12 (dd, 1H, $J_{9a\ 9b}$ = 12.3 Hz, H-9a), 3.98−4.10 (m, 3H, $J_{5,6}$ = 10.4 Hz, $J_{6',7'}$ = 1.2 Hz, H-5, 5′, 6′), 3.95 (dd, 1H, H-9′b), 3.87 (s, 3H, OCH_3), 3.44 (dd, 1H, H-9b), 3.41 (s, 3H, OCH_3), 2.86 (dd,1H, $J_{3e,4}$ = 4.9 Hz, $J_{3e,3a}$ = 13.6 Hz, H-3e), 2.82 (dd, 1H, $J_{3'e,\ 4'}$ = 8.5 Hz, $J_{3'e,\ 3'a}$ = 12.9 Hz, H-3′e), 2.24, 2.05, 2.03, 2.02, 2.00 (6s, 18H, OCOCH_3), 2.17 (dd, 1H, H-3a), 2.05 (dd, 1H, H-3′a); ^{13}C NMR (^{1}H) δ 75.0, 72.9, 72.7, 71.6, 69.9, 69.0, 68.5, 68.1, 66.3, 61.8, 53.5, 52.2, 49.9, 50.5, 38.9, 38.3

Methyl *O*-(Methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-(2 → 8)-*O*-(methyl 4,7-di-*O*-acetyl-9-*O*-benzyl-3,5-dideoxy-5-trifluoroacetamido-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonate)-(2 → 3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (13). A mixture of donor **12** (37 mg, 0.03 mmol), **8b** (25.5 mg, 0.03 mmol), and activated molecular sieves (3 Å, 200 mg) in MeCN (1.5 mL) was stirred for 16 h under an atmosphere of argon. The mixture was cooled to −35 °C, NIS (0.06 mmol) and TfOH (6.3 μmol) were added, and the reaction mixture was stirred for 30 min until TLC analysis indicated that reaction had gone to completion. The reaction mixture was diluted with DCM (5 mL), the solids were filtered off, and the residue was washed with DCM (3 × 5 mL). The combined filtrate (20 mL) was washed with aqueous $Na_2S_2O_3$ (20%, 7 mL) and H_2O (3 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by size exclusion column chromatography on Sephadex LH-20 (methanol/dichloromethane, 1/1, v/v) to **13** as a white foam (23.5 mg, 42%): FAB MS *m*/*z* 1889.6 $[M + Na]^+$; R_f 0.69 (ethyl acetate/hexane, 3/2, v/v); $[\alpha]^{27}_D = +4.6$ (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.61 (d, 1H, $J_{NH,5''}$ = 9.8 Hz, NH), 7.14−7.37 (m, 30H, aromatic), 6.16 (d, 1H, $J_{NH,5'''}$ = 9.2 Hz, NH), 5.50−5.56 (m, 1H, $J_{8''',9'''a}$ = 2.4 Hz, $J_{8''',9'''b}$ = 4.9 Hz, H-8‴), 5.27 (dd, 1H, $J_{7''',8'''}$ = 9.8 Hz, H-7‴), 5.20 (s, 1H, H-7′), 5.06 (d, 1H, H-8″), 4.92−5.03 (m, 2H, $J_{4'',5''}$ = 10.7 Hz, $J_{4''',5'''}$ = 10.3 Hz, H-4″, 4‴), 4.81 (dd, 2H, J^2 = 10.7 Hz, CH_2Ph), 4.75 (dd, 2H, J^2 = 10.7 Hz, CH_2Ph), 4.70 (dd, 2H, J^2 = 11.7 Hz, CH_2Ph), 4.30−4.56 (m, 6H, CH_2Ph) 4.39 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 4.34 (dd, 1H, $J_{6''',7'''}$ = 1.9 Hz, H-6‴), 4.28 (dd, 1H, $J_{9'''a,9'''b}$ = 12.7 Hz, H-9‴a), 4.26 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 4.22 (dd, 1H, $J_{9''a,9''b}$ = 11.7 Hz, H-9″a), 4.20 (dd, 1H, H-9‴b), 4.04 (dd, 1H, $J_{5'',6''}$ = 10.7 Hz, H-5″), 4.00 (dd, 1H, $J_{6''',7'''}$ = 1.5 Hz, H-6‴), 3.97 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, H-3′), 3.92 (t, 1H, $J_{5''',6'''}$ = 10.3 Hz, H-5‴), 3.65−3.86 (m, 4H, H-4, 4′, 6), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.42−3.60 (m, 4H, $J_{2',3'}$ = 9.3 Hz, H-2′, 3, 6′a, 9″b), 3.30−3.40 (m, 3H, H-2, 5, 6′b), 3.12 (t, $J_{5',6'a}$ = 6.3 Hz, H-5′), 2.75 (dd, 1H, $J_{3'''e,3'''a}$ = 13.2 Hz, $J_{3'''e,4'''}$ = 4.9 Hz, H-3‴e), 2.60 (dd, 1H, $J_{3''e,3''a}$ = 13.2 Hz, $J_{3''e,4''}$ = 4.8 Hz, H-3″e), 2.41(s, 1H, OH), 2.01 (m, 1H, 3″a), 1.98 (m, 1H, 3‴a), 2.17, 2.03, 1.98, 1.97, 1.90, 1.86 (6s, 18H, OCOCH_3); ^{13}C NMR δ 170.0, 168.8, 168.3, 138.9, 138.7, 138.5, 138.3, 128.6, 128.4, 128.3, 128.1, 127.9, 127.6, 127.4, 104.8, 102.5, 98.9, 96.8, 83.0, 82.1, 76.7, 7.4, 75.6, 75.1, 74.8, 74.2, 73.6, 73.5, 73.3, 72.5, 71.6, 70.6, 69.4, 69.2, 68.7, 68.5, 68.4, 67.9, 66.8, 62.4, 57.3, 53.7, 53.4, 50.1, 50.0, 39.1, 36.7, 21.6, 20.9, 20.8, 20.6.

Methyl *O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-(2 → 8)-*O*-(5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosylonic acid)-(1 → 3)-*O*-β-D-galactopyranosyl)-(1 → 4)-β-D-glucopyranoside Disodium Salt (14). Compound **13** (13 mg, 7 μmol) was dissolved in ethanol/ethyl acetate (2 mL, 1/1, v/v), and $Pd(OAc)_2$ (13 mg) was added. The mixture was stirred under an atmosphere of H_2 for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in MeOH (1 mL), and 1 M aqueous NaOH (0.3 mL) was added dropwise. After 72 h (control TLC, methanol/*n*-buthanol/water/triethylamine, 20/60/15/5, v/v/v/v) the reaction mixture was concentrated in vacuo ,and the residue was subjected to freeze-drying for 16 h. MeOH (0.5 mL) and Ac_2O (0.1 mL) were added, and the reaction mixture was kept for 6 h and then concentrated under the reduced pressure. The residue was purified by size exclusion column chromatography on Sephadex G25 (35 cm^3, water elution) to afford **14** as white foam (4.4 mg, 71%): FAB MS *m*/*z* 983.3 $[M + H]^+$; R_f 0.40; $[\alpha]^{27}_D = +3.4$ (*c* 0.5, H_2O); ^{1}H NMR (D_2O) δ 4.40 (d, 1H, $J_{1',2'}$ = 8.3 Hz, H-1′), 4.20 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1), 4.06 (dd, 1H, $J_{9''a,9''b}$ = 12.2 Hz, H-9″a), 4.00−4.03 (m, 1H, $J_{8''',9'''a}$ = 2.4 Hz, $J_{8''',9'''b}$ = 5.4 Hz, H-8‴), 3.97 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, H-3′), 3.91 (dd, 1H, $J_{9'''a,9'''b}$ = 12.2 Hz, H-9‴a), 3.84 (d, 1H, H-4′), 3.42−3.82 (m, 20 H, H-2′, 3, 4, 4″, 4‴, 5, 5′, 5″, 5‴, 6, 6′, 6″, 6‴, 7″, 7‴, 8″, 9″b, 9‴b), 3.45 (s, 3H, OCH_3), 3.19 (t, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 2.66 (dd, 1H, $J_{3'''e,3'''a}$ = 12.2 Hz, $J_{3'''e,4'''}$ = 4.4 Hz, H-3‴e), 2.56 (dd, 1H, $J_{3''e,3''a}$ = 12.2 Hz, $J_{3''e,4''}$ = 4.4 Hz, H-3″e), 1.95, 1.91 (2s, 6H, NHCOCH_3), 1.58−1.66 (m, 2H, H-3″a,3‴a); ^{13}C NMR (D_2O) δ 181.5, 175.1, 162.8, 103.3, 102.9, 100.7, 100.4, 78.4, 75.7, 75.4, 75.0, 74.2, 73.1, 72.9, 71.9, 69.6, 68.7, 68.4, 62.8, 61.8, 61.3, 60.2, 57.5, 52.5, 52.0, 40.7, 40.0, 22.6, 22.3.

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Supporting Information Available: Copies of NMR spectra for compounds **2a**, **3**, **5a**, **6a**−**c**, **7**, **9**, **10**, and **12**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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